Practice Implications of the Atrial Fibrillation Guidelines

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Atrial fibrillation is one of the most common and complex cardiac arrhythmias. Using currently available evidence, leading medical societies have established recommendations for the optimal management of atrial fibrillation. These guidelines have recently been updated by 4 consensus groups: the European Society of Cardiology, the American College of Chest Physicians, the Canadian Cardiovascular Society, and a task force of 3 societies from the United States: the American College of Cardiology Foundation, the American Heart Association, and the Heart Rhythm Society. The present review focused on the similarities and differences among these recently updated guidelines. Key revisions included updated information on newer treatments for rhythm control, treatment options to reduce atrial fibrillation complications, and updated anticoagulant management for thromboprophylaxis.

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An estimated 3 million Americans and 4.5 million Europeans are affected by atrial fibrillation (AF).[1,2] By 2050, a projected 6 to 16 million Americans will be affected by this arrhythmia, with similar increases expected in Europe.[2,3] Leading medical societies periodically evaluate medical evidence to provide guidance on the best practices for clinicians. The guidelines for the management of AF have recently been updated by 4 separate consensus groups: the European Society of Cardiology (ESC), the American College of Chest Physicians (ACCP), the Canadian Cardiovascular Society (CCS), and a task force of 3 societies from the United States: the American College of Cardiology Foundation, American Heart Association, and Heart Rhythm Society (ACCF/AHA/HRS).[4−15] These new guidelines include updated information on newer treatments for rhythm control and treatments to reduce AF complications. Given that much of the morbidity and mortality in AF is due to stroke and thromboembolism, thromboprophylaxis is critical to reduce the embolic risk.[16] Despite these recommendations, many patients with AF do not receive appropriate thromboprophylaxis.[17−19] This underuse of thromboprophylaxis might be in part because of the dosing complexities of the anticoagulant warfarin. New options for anticoagulation for patients with AF have recently become available and have been described in the new guidelines.

The present review focused on the similarities and differences among this quartet of updated guidelines, highlighting the ACCF/AHA/HRS recommendations and comparing them with the ESC, ACCP, and CCS guidelines.

Methodology Updates

The classification of recommendations and ranking of evidence in the ACCF/AHA/HRS, ESC, ACCP, and CCS guidelines are listed in Tables 1 and 2. The updated ACCF/AHA/HRS methodology separates class III recommendations into 2 subclasses to delineate whether the recommendation is determined to be of "no benefit" or associated with "harm" to the patient.[14] The CCS also updated its methodology, introducing the Grading of Recommendations Assessment Development and Evaluation system for the classification of recommendations and ranking the evidence level.[12] The ACCP also uses the Grading of Recommendations Assessment Development and Evaluation system, differing only in that the quality of a body of evidence can be high (A), moderate (B), or low (C).[20] For the ninth edition ACCP guidelines (2012), in addition to experts in the field of thrombosis, clinician experts in methodology and the interpretation of evidence were added to the panel and provided the primary leadership responsibilities, allowing a more rigorous application of the ACCP Grading of Recommendations Assessment Development and Evaluation approach than previously.[20,21]

Criteria for Rate Control

The parameters for optimal rate control in patients with AF are controversial and have no standard method of assessment. The new ACCF/AHA/HRS guidelines include a change in the recommended target heart rate—stating that treatment to achieve strict control of the heart rate is not beneficial compared with lenient control. The European and Canadian recommendations have made similar changes, with subtle differences (Table 3).

This change in the recommended target heart rate was largely determined from the results of the Rate Control Efficacy in Permanent Atrial Fibrillation (RACE II) study. The RACE II study found that strict heart rate control in patients with AF was not beneficial compared with lenient control (strict rate control: a heart rate at rest of <80 beats/min and <110 beats/min during moderate exercise; lenient rate control: a heart rate at rest of <110 beats/min). A larger proportion of patients treated with the lenient strategy achieved their target heart rate goal, with lower drug doses and fewer drug combinations, resulting in far fewer outpatient visits to achieve the intended target.[14,22] In general, lenient rate control is more convenient (requires

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Table 1
Classification/grading of recommendations assessment development and evaluation of recommendations*

ACCF/AHA/HRS	ESC	AACP	CCS
Class I Conditions for which there is evidence and/or general agreement that a given procedure/therapy is beneficial, useful, and effective	Class I Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, and effective	Grade 1 (strong) Benefits clearly outweigh risk and burdens or vice versa	Strong
Class II Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of performing the procedure/therapy	Class II Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure	Grade 2 (weak) Benefits closely balanced with risks and burden	Conditional (i.e., weak)
Class IIa Weight of evidence/opinion is in favor of usefulness/efficacy	Class IIa Weight of evidence/opinion is in favor of usefulness/efficacy		
Class IIb Usefulness/efficacy is less well established by evidence/opinion	Class IIb Usefulness/efficacy is less well established by evidence/opinion		
Class III Conditions for which there is evidence and/or general agreement that a procedure/therapy is not useful or effective and in some cases could be harmful	Class III Evidence or general agreement that the given treatment or procedure is not useful/effective, and in some cases could be harmful		
COR III—no benefit Not useful/effective, no proven benefit			
COR III—harm Could be harmful to patient or excess cost without benefit			

COR = class of recommendation; GRADE = Grading of Recommendations Assessment, Development, and Evaluation.
* Size of treatment effect from top of Table 1 to bottom.

Table 2
Level/quality of evidence and the strength of recommendation

Level of evidence	ACCF/AHA/HRS	ESC	AACP	CCS*
A (high)	Data derived from multiple randomized clinical trials or meta-analyses	Data derived from multiple randomized clinical trials or meta-analyses	Consistent evidence from randomized controlled trials without important limitations or exceptionally strong evidence from observational studies	High; future research unlikely to change confidence in estimate of effect (e.g., multiple well-designed, well-conducted clinical trials)
B (moderate)	Data derived from a single randomized trial or nonrandomized studies	Data derived from a single randomized clinical trial or large nonrandomized studies	Evidence from randomized controlled trials with important limitations (inconsistent results, methodologic flaws, indirect or imprecise) or very strong evidence from observational studies	Moderate; additional research likely to have an important effect on confidence in estimate of effect and might change the estimate (e.g., limited clinical trials, inconsistency of results or study limitations)
C (low)	Only consensus opinion of experts, case studies, or standard-of-care	Consensus of opinion of experts and/or small studies, retrospective studies, registries	Evidence for at least 1 critical outcome from observational studies, case series, or randomized controlled trials, with serious flaws or indirect evidence	Low; additional research very likely to have a significant effect on estimate of effect and likely to change estimate (e.g., small number of clinical studies or cohort observations)
—	—	—	—	Very low; estimate of effect very uncertain (e.g., case studies, consensus opinion)

* The CCS uses the GRADE system for ranking the level of evidence (high, moderate, low, very low). The CCS also uses other factors in determining the strength of the recommendation: (1) difference between desirable and undesirable effects (the greater the difference between the desirable and undesirable effects, the greater the probability that a strong recommendation is indicated); (2) values and preferences (the greater the variation or uncertainty in values and preferences, the greater the probability that a conditional recommendation is indicated); (3) cost (the greater the cost, the lower the likelihood that a strong recommendation is indicated).

Table 3
New American College of Cardiology Foundation (ACCF)/American Heart Association (AHA)/Heart Rhythm Society (HRS) recommendations compared with European Society of Cardiology (ECS), American College of Chest Physicians (ACCP), and Canadian Cardiovascular Society (CCS) recommendations

New Recommendation	ACCF/AHA/HRS	ESC	ACCP	CCS
Heart rate control	Strict rate control (<80 beats/min at rest, <110 beats/min during moderate exercise) not beneficial compared with lenient rate control (<110 beats/min at rest)* (class III—no benefit; level of evidence B)	Initially, lenient rate control, heart rate at rest of <110 beats/min (class IIa; level of evidence B); if symptoms persist or tachycardiomyopathy occurs, use stricter rate control (class IIa; level of evidence B)	NR	Rate control should aim for heart rate at rest of <100 beats/min (strong; high-quality evidence)
Combining anticoagulant therapy with antiplatelet therapy	Clopidogrel plus aspirin if OAC is unsuitable (class IIb; level of evidence B); triple therapy generally not recommended	Clopidogrel plus aspirin only if patients refuse OAC and bleeding risk is low (class IIa; level of evidence B); triple therapy: (1) after stenting if thromboembolic risk is moderate to high; (2) in short term after ACS or PCI† (class IIa; level of evidence C)	Triple therapy after stent placement if $CHADS_2$ ≥2 (grade 2C)	Triple therapy after ACS or PCI if risk of stroke is high (conditional; low-quality evidence)
Dronedarone	Is reasonable in patients with paroxysmal AF or after conversion of persistent AF (class IIa; level of evidence B); not for patients with class IV heart failure or patients with recent decompensated heart failure (class III—harm; level of evidence B)	Is reasonable to achieve rate control in patients with recurrent AF (class I; level of evidence A); not for patients with NYHA class III to IV or unstable heart failure (class III; level of evidence B); not for patients in permanent AF (class III)	NR	Can be used along with other agents to optimize rate control (conditional; moderate-quality evidence); not for patients in permanent AF, with a history of heart failure, or LVEF ≤0.40, and not for the sole purpose of rate control (strong; high-quality evidence)
Dabigatran	An alternative to warfarin in patients without prosthetic heart valves or hemodynamically significant disease, renal failure, or advanced liver disease (impaired baseline clotting function); 150 mg twice daily in patients with creatinine clearance >30 ml/min; 75 mg twice daily in patients with creatinine clearance 15−30 ml/min (class I; level of evidence B)	Dabigatran, rivaroxaban,‡ or apixaban‡ in preference to warfarin (class IIa; level of evidence A) Dabigatran 150 mg twice daily for most patients; 110 mg twice daily for patients ≥80 yrs old, concomitant use of interacting drugs (e.g., verapamil), HAS-BLED score ≥3, or in patients with creatinine clearance 30−49 ml/min (class IIa; level of evidence B)	150 mg twice daily rather than VKA, except for patients with AF and mitral stenosis, stent, or $CHADS_2$ ≥1 who experience ACS (grade 2B)	Dabigatran, rivaroxaban,§ or apixaban§ in preference to warfarin Dabigatran 150 mg twice daily preferable to 110 mg twice daily, except in certain patients¶ (conditional; high-quality evidence)
Catheter-based ablation therapy for maintenance of sinus rhythm	For significantly symptomatic, paroxysmal AF refractory to antiarrhythmic drugs in some patients‖ (class I; level of evidence A); for symptomatic persistent AF (class IIa; level of evidence A); for symptomatic, paroxysmal AF in patients with significant left atrial dilation or with significant LV dysfunction (class IIb; level of evidence A)	For symptomatic, paroxysmal AF refractory to antiarrhythmic drugs (class I; level of evidence A); first-line treatment of certain patients with AF (class IIa, level of evidence B); antiarrhythmic drugs not a prerequisite in AF patients who remain symptomatic despite rate-control drugs and no significant underlying heart disease (class IIb; level of evidence B); for patients with heart failure and AF refractory to antiarrhythmic drugs (class IIb; level of evidence B)	NR#	For AF refractory to antiarrhythmic drugs in patients in whom rhythm control remains desired (strong; moderate-quality evidence); first-line therapy in highly selected patients with symptomatic, paroxysmal AF (conditional; low-quality evidence)

ACS = acute coronary syndrome; HAS-BLED = hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio, elderly, and drugs/alcohol; LV = left ventricular; LVEF = left ventricular ejection fraction; NR = no recommendation provided in published guidelines; NYHA = New York Heart Association; OAC = oral anticoagulant therapy; PCI = percutaneous coronary intervention; triple therapy = combination of vitamin K antagonist, aspirin, and clopidogrel; VKA = vitamin K antagonist therapy.

* In patients with permanent AF with LVEF >0.4 and no or acceptable symptoms related to arrhythmia.

† At 3−6 months after ACS with or without PCI; 4 weeks after elective PCI.

‡ Rivaroxaban was approved for use in Europe in December 2011; the 2012 ECS update has recommended rivaroxaban and included apixaban once approved in Europe (approved in November 2012).

§ Approval for rivaroxaban was obtained in Canada January 2012; the 2012 CCS focused update included rivaroxaban and recommended apixaban once approved by Health Canada (approved in December 2012).[44,45]

¶ Patients of low body weight, decreased renal function, or at increased risk of major bleeding.

‖ Patients with normal or mildly dilated left atria, normal or mildly reduced LV function, and no severe pulmonary disease.

The ACCP does not provide specific recommendations for catheter-based ablation in the management of AF.

fewer outpatient visits and examinations) and easier to achieve. Thus, lenient rate control might be a reasonable strategy for patients with permanent AF.

The ACCF/AHA/HRS, ESC, and CCS guidelines have all stated that strict rate control is no longer considered superior to lenient rate control (Table 3).[9,13,14] However, the CCS has recommended a heart rate target of <100 beats/min at rest for most patients. This conservative target heart rate might have been in response to the relatively small number of patients in the RACE II trial randomized to the lenient rate control group with a heart rate at rest of >100 to 110 beats/min. Thus, the safety of a heart rate at rest of >100 beats/min might not have been conclusively demonstrated. Additionally, at the end of the first year of the RACE II trial, the difference in the heart rate between the lenient and strict rate-control groups was actually quite small (mean ± SD heart rate at rest of 86 ± 15 and 75 ± 12 beats/min in the lenient and strict rate-control arms, respectively).[23]

The updated ACCP guidelines do not provide criteria for a target heart rate or specific recommendations for rate-control strategies. Previous ACCP guidelines ("Pharmacologic Control of Ventricular Rate," 2005) provided clinical recommendations for pharmacologic rate control of AF and atrial flutter, but they do not specify a target heart rate.[24]

Rhythm-Control Strategy

The new ACCF/AHA/HRS guidelines found no benefit in a routine rhythm-control strategy for patients with AF with systolic heart failure compared with a rate-control strategy. This recommendation was determined from the Atrial Fibrillation and Congestive Heart Failure Trial, which found that a routine rhythm-control strategy did not reduce the death rate from cardiovascular causes compared with a rate-control strategy in patients with AF and congestive heart failure.[25] In that study, rhythm-control therapy included electrical cardioversion in patients who did not achieve sinus rhythm after antiarrhythmic drug therapy, repeat cardioversion if needed, and possible referral for nonpharmacologic therapy. Amiodarone was the antiarrhythmic drug of choice, and either sotalol or dofetilide was used if necessary. Rate-control therapy included adjusted doses of β blockers with digitalis to achieve the targeted heart rate (<80 beats/min at rest or <110 beats/min during a 6-minute walk).The primary end point (death from cardiovascular causes) was not significantly different between the rhythm-control (27%) and rate-control (25%) strategies (mean follow-up 37 months; hazard ratio [HR] for rhythm-control group 1.06, 95% confidence interval [CI] 0.86 to 1.30, p = 0.59, log-rank test).[14,25]

The CCS has recommended a rhythm-control strategy for patients with AF who remain symptomatic with rate-control therapy or in whom rate-control therapy is unlikely to control their symptoms.[9] Similarly, the ESC has recommended that rhythm-control therapy can be added to rate-control therapy if the patient is symptomatic despite adequate rate control, or if a rhythm-control strategy is selected because of factors such as the degree of symptoms, younger age, or greater activity levels.

Additionally, the ACCF/AHA/HRS has recommended that permanent AF be managed by rate control, unless it is deemed possible to restore sinus rhythm. Paroxysmal AF can be managed by rate-control or rhythm-control therapy. The latter is especially attractive in highly symptomatic patients with little or no associated underlying heart disease.[26]

Although the ACCP did not provide specific recommendations for rhythm-control therapy in patients with AF, they noted that the results of the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) trial indicated that patients with AF at high risk of stroke generally benefit from anticoagulation even after sinus rhythm has been restored.[15,27] The ACCP has recommended that long-term antithrombotic therapy be determined by the patient's underlying risk of stroke and not the underlying rhythm.

Stroke Prevention: New Recommendations for Combining Anticoagulant With Antiplatelet Therapy

In patients with AF in whom oral anticoagulation therapy with warfarin is unsuitable, the ACCF/AHA/HRS has recommended that the addition of clopidogrel to aspirin to reduce the risk of major vascular events, including stroke, *could be considered*. The basis for this recommendation was the results from the Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events (ACTIVE W) and Effect of Clopidogrel Added to Aspirin in Patients with Atrial Fibrillation (ACTIVE A) trials.[28,29] The results of the ACTIVE W trial indicate that oral antithrombotic therapy with aspirin (75 to 100 mg/day) plus clopidogrel (75 mg/day) was inferior to warfarin (target international normalized ratio 2.0 to 3.0) for the prevention of vascular events in patients eligible for either therapeutic approach (primary events, relative risk [RR] 1.44, 95% CI 1.18 to 1.76, p = 0.0003). The results of the ACTIVE A trial have indicated that aspirin plus clopidogrel reduced the risk of major vascular events (clopidogrel, RR 0.89, 95% CI 0.81 to 0.98, p = 0.01), especially stroke (RR 0.72, 95% CI 0.62 to 0.83, p <0.001), and increased the risk of major hemorrhage (RR 1.57, 95% CI 1.29 to 1.92, p <0.001) compared with aspirin alone in patients with AF considered unsuitable for oral anticoagulation therapy with warfarin.

In November 2012, the ECS published a focused update to the 2010 ECS guidelines.[30] Given the availability of new oral anticoagulation therapy, the ESC has now recommended that aspirin plus clopidogrel therapy for stroke prevention in AF should be limited to patients who refuse oral anticoagulation therapy.

The ACCP has recommended combination therapy with aspirin plus clopidogrel for patients with AF who are unsuitable for, or who choose not to take, oral anticoagulation therapy (for reasons other than concerns about major bleeding).

In contrast, the CCS has not recommended aspirin plus clopidogrel therapy for patients with AF for whom warfarin is considered unsuitable. In such cases, the CCS has recommended the use of dabigatran, because it might reduce the risk of stroke at a lower risk of bleeding compared with warfarin.[6,31,32] In fact, the CCS has recommended that dabigatran should be preferred to warfarin in most patients who need antithrombotic therapy for AF. The CCS has also noted that the bleeding risk is very similar or even increased

Table 4
Key clinical trials with dronedarone

Study	Full Study Name	Key Findings
ADONIS[34]	American-Australian-African Trial With Dronedarone in Atrial Fibrillation or Flutter Patients for the Maintenance of Sinus Rhythm	Dronedarone was significantly more effective than placebo in maintaining sinus rhythm; dronedarone prolonged time to recurrence of AF (HR 0.75, p <0.001)
ANDROMEDA[35]	Antiarrhythmic Trial with Dronedarone in Moderate to Severe CHF Evaluating Morbidity Decrease	Dronedarone increased early mortality in patients with recently decompensated heart failure and depressed LV function (median follow-up time 2 mos, HR 2.13, p = 0.03)
ATHENA[36,37]	A placebo-controlled, double-blind, parallel-arm Trial to assess the efficacy of dronedarone 400 mg twice daily for the prevention of cardiovascular Hospitalization or death from any cause in patiENts with Atrial fibrillation/atrial flutter	Dronedarone reduced death and cardiovascular hospitalizations in patients with paroxysmal or persistent AF, or atrial flutter and risk factors for thromboembolism (HR 0.76, p <0.001); fewer strokes occurred in the dronedarone group, although this effect was not prespecified and requires confirmation by other trials (HR 0.66, p = 0.027)*
DAFNE[38]	Dronedarone Atrial FibrillatioN study after Electrical cardioversion	Administration of dronedarone in patients with persistent AF converted only 5.8% to sinus rhythm (3.1% converted with placebo) and did not improve acute success of electrical cardioversion; increased time to AF relapse with dronedarone 800 mg (RR 55%, p = 0.001)
DIONYSOS[39]	Efficacy and Safety of Dronedarone Versus Amiodarone for the Maintenance of Sinus Rhythm in Patients With Persistent Atrial Fibrillation	Dronedarone was less effective than amiodarone in decreasing AF recurrence in patients with persistent AF (recurrence of AF, HR 1.59, p <0.0001), but it was better tolerated
EURIDIS[34]	European Trial In Atrial Fibrillation or Flutter Patients Receiving Dronedarone for the Maintenance of Sinus Rhythm	Dronedarone was significantly more effective than placebo in maintaining sinus rhythm; dronedarone prolonged time to recurrence of AF (HR 0.78, p = 0.01)
PALLAS[40,41]	Permanent Atrial fibriLLAtion outcome Study using dronedarone on top of standard therapy	Trial stopped early because of twofold increase of cardiovascular adverse events in patients receiving dronedarone compared with patients receiving placebo; final results show dronedarone significantly increased stroke (HR 2.32, p = 0.02), heart failure (HR 2.16, p <0.001), death (HR 1.94, p = 0.049), and unplanned cardiovascular hospitalization (HR 1.97, p <0.001) compared with placebo

CHF = congestive heart failure; LV = left ventricular.
* The ATHENA trial excluded patients with decompensated heart failure within the previous 4 weeks or with class IV heart failure.

with aspirin plus clopidogrel compared with anticoagulation with warfarin.[6,32]

For patients with a history of AF who have recently undergone percutaneous coronary intervention, the CCS has recommended a period of triple therapy (combined use of warfarin with dual antiplatelet therapy) for optimal prophylaxis in patients at a high risk of stroke.[6] The guidelines deferred specification of the duration of the triple therapy, indicating that the decision should be determined by balancing the risk of a stent-related event and the risk of bleeding.

The ESC concluded that triple therapy might have an acceptable risk/benefit ratio, provided the duration of treatment is short and the bleeding risk is low. Triple therapy is recommended for patients with AF after coronary artery stenting in situations with moderate to high thromboembolic risk. The duration of treatment should be similar to dual therapy, except that the times are all shortened because of the bleeding risks associated with long-term triple therapy. For bare metal stents, 1 month of triple therapy is appropriate; however, drug-eluting stents require ≥3 months (for the "-olimus" group: sirolimus, everolimus, tacrolimus) or ≥6 months (paclitaxel) of triple therapy. Triple therapy has also been recommended in the initial period (3 to 6 months) after an acute coronary syndrome with or without percutaneous coronary intervention.[13]

Similarly, the ACCP has recommended triple therapy (vitamin K antagonist, aspirin, and clopidogrel) for patients with AF at a high risk of stroke ($CHADS_2$ [congestive heart failure, hypertension, age 75 years or older, diabetes, previous stroke/transient ischemic attack/thromboembolism] score ≥2) during the first month after placement of a bare metal stent or the first 3 to 6 months after placement of a drug-eluting stent (i.e., when the risk of stent thrombosis is greatest.).[15] The guidelines noted that patients with AF who have received a drug-eluting stent and who are at increased risk of late stent thrombosis (e.g., acute coronary syndrome at presentation, diabetes, long lesions, narrow diameter of target vessel)[33] might choose to continue triple therapy for a full 12 months after stent placement if they place a low value on avoiding bleeding.

The ACCF/AHA/HRS did not make specific recommendations regarding triple therapy for patients with AF and stents. The guidelines only noted that this strategy has been associated with an increase in bleeding complications that can range from mild or moderate to severe or life-threatening and that no prospective randomized controlled trials have been reported addressing the bleeding risk of combination therapy.[32,34]

New Recommendations for Dronedarone

The ACCF/AHA/HRS, ESC, and CCS have now included the use of dronedarone in the management of AF.

Table 5
HAS-BLED (hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio, elderly, and drugs/alcohol) bleeding risk score

Letter	Clinical Characteristic	Assigned Points
H	Hypertension*	1
A	Abnormal renal and liver function (1 point each)†	1 or 2
S	Stroke	1
B	Bleeding‡	1
L	Labile INRs§	1
E	Elderly (age >65 yrs)	1
D	Drugs or alcohol (1 point each)‖	1 or 2

INR = international normalized ratio.

* Hypertension is defined as systolic blood pressure of >160 mm Hg.

† Abnormal kidney function defined as the presence of chronic dialysis, renal transplantation, or serum creatinine of ≥200 mmol/L; abnormal liver function defined as chronic hepatic disease (e.g., cirrhosis) or biochemical evidence of significant hepatic derangement (e.g., bilirubin 2 times the upper limit of normal, in association with aspartate aminotransferase/alanine aminotransferase/alkaline phosphatase 3 times the upper limit of normal).

‡ Bleeding refers to bleeding history and/or predisposition to bleeding (e.g., bleeding diathesis, anemia).

§ Labile INRs refers to unstable/high INRs or poor time in therapeutic range (e.g., 60%).

‖ Drug/alcohol use refers to concomitant use of drugs, such as antiplatelet agents, nonsteroidal anti-inflammatory drugs, or alcohol abuse.

The ACCP guidelines do not mention the use of dronedarone. The new ACCF/AHA/HRS guidelines have indicated that dronedarone might decrease the need for hospitalizations for cardiovascular events in patients with paroxysmal AF or after conversion of persistent AF. However, dronedarone is not recommended for patients with class IV heart failure or patients who have had an episode of decompensated heart failure in the previous 4 weeks, especially in the presence of depressed left ventricular function (left ventricular ejection fraction ≤35%).[14] The recommendations regarding dronedarone use were based on the results from several recent clinical trials[35–42] (Table 4).

The results of the Permanent Atrial fibriLLAtion Outcome Study Using Dronedarone on Top of Standard Therapy (PALLAS) trial, published after the guidelines were updated, have demonstrated that dronedarone is detrimental in patients with permanent AF[42] (Table 4). Thus, dronedarone should be reserved for selected low-risk patients with persistent or paroxysmal AF, possibly those in whom other antiarrhythmic drugs have failed, when the intention is to maintain sinus rhythm.[43,44]

The 2012 ESC focused update has strengthened its guideline that dronedarone should not be used in class III to IV or unstable heart failure. Although dronedarone is useful to decrease the heart rate at rest and with exercise during AF relapses, it is contraindicated in patients with permanent AF.[13,30] The ESC has also advised that dronedarone management should be supervised by a specialist (i.e., hospital or office-based staff familiar with the use of antiarrhythmic drugs).

In March 2012, the CCS published a focused update to the 2010 CCS guidelines. Based largely on the results of the PALLAS trial, the update added the recommendations that dronedarone (1) should not be used in patients with permanent AF nor for the sole purpose of rate control, (2) should not be used in patients with a history of heart failure or a left ventricular ejection fraction ≤0.40, and (3) should be used with caution in patients taking digoxin.

Updated Recommendations for Catheter-Based Ablation Therapy for Maintenance of Sinus Rhythm in AF

The ACCF/AHA/HRS has expanded the recommendations on the use of catheter-based ablation in the management of AF.[14] Catheter ablation is recommended for patients (1) with symptomatic, paroxysmal AF in whom ≥1antiarrhythmic drug has failed, (2) with symptomatic, persistent AF, and (3) with symptomatic, paroxysmal AF with significant left atrial dilation or significant left ventricular dysfunction.[14] The ACCF/AHA/HRS also added a new section on the future directions of catheter-based ablation in the management of AF.

The ACCF/AHA/HRS, ESC, and CCS are in general agreement that catheter ablation should be reserved for symptomatic patients with paroxysmal AF, although differences were present in the determination of the criteria for select patient populations. Similar to the ACCF/AHA/HRS, the CCS has recommended catheter ablation for patients who remain symptomatic during antiarrhythmic drug therapy and for whom rhythm control remains desirable. The CCS has also suggested catheter ablation as the first-line therapy for *highly selected* patients with symptomatic, paroxysmal AF (i.e., patients with a strong intolerance or aversion to antiarrhythmic drugs).

The ESC guidelines have elevated catheter ablation to first-line treatment of some patients and did not specify a trial of antiarrhythmic medication as a prerequisite. As an alternative to antiarrhythmic drugs, catheter ablation can be offered to patients with paroxysmal AF and no or minimal heart disease who continue to be highly symptomatic despite rate-control medications. The 2012 focused update upgraded these recommendations but restricted them to experienced centers/investigators, appropriate patient selection, careful evaluation of treatment alternatives, and patient preference. The guidelines characterized catheter ablation for persistent and long-standing persistent AF as being "less well established."

The ACCP guidelines do not provide specific recommendations for the use of catheter-ablation therapy in the management of AF. The guidelines observed that in randomized controlled trials, although catheter ablation was found to significantly reduce AF recurrence at ~1 year of follow-up, the AF recurrence rate ranged from 11% to 44% at ~1 year. Because of the results of the AFFIRM trial, the lack of longer term follow-up data from catheter ablation randomized controlled trials regarding AF recurrence rates, and the poor reporting of stroke outcomes, the ACCP has recommended that for patients with AF receiving catheter ablation (or other rhythm-control strategies), decisions about long-term antithrombotic therapy should be determined by the underlying risk of stroke and not the underlying rhythm.

New Recommendations for Dabigatran

With approval by the Food and Drug Administration for dabigatran etexilate (Pradaxa, Boehringer Ingelheim Pharma GmbH, Biberach an der Riss, Germany) to reduce the risk of

Table 6
Recommendations for risk assessment guiding choice of antithrombotic therapy

$CHADS_2$ score	Recommended Therapy for Patients With AF			
	ACCF/AHA/HRS	ESC*	ACCP	CCS
0	Aspirin, 81−325 mg/day	No antithrombotic therapy	Aspirin, 75−325 mg/day or no antithrombotic therapy; no antithrombotic therapy is preferred over aspirin	Aspirin, 75−325 mg/day
1	Aspirin, 81−325 mg/day, or warfarin (INR 2.0−3.0, target 2.5) or dabigatran	No antithrombotic therapy (if age <65 yrs and lone AF) or OAC. Dabigatran, rivaroxaban, apixaban,† or warfarin (INR 2.0−3.0); determined by assessment of risk of bleeding complications and patient preference	OAC (INR 2.0−3.0). Dabigatran is suggested. For patients unsuitable for, or who choose not to take, an OAC, combination therapy with clopidogrel and aspirin (75−325 mg/day) preferred over aspirin alone	OAC. Dabigatran, rivaroxaban, or apixaban‡ according to individual risk/benefit considerations; aspirin is a reasonable alternative for some patients
≥2	Warfarin (INR 2.0−3.0, target 2.5) or dabigatran	OAC. Dabigatran, rivaroxaban, or apixaban† in preference to warfarin (INR 2.0−3.0), based on the patient's net clinical benefit	OAC (INR 2.0−3.0). Dabigatran in preference to warfarin, if severe renal impairment absent. If OAC is unsuitable or not patient choice, combination therapy with clopidogrel and aspirin (75−325 mg/day)	OAC. Dabigatran, rivaroxaban, and apixaban‡ are preferred over warfarin for most patients

INR = international normalized ratio; OAC = oral anticoagulation therapy.
* For ESC, score refers to CHA_2DS_2-VASc score.
† In the 2012 focused update of the ESC guidelines, apixaban was included for stroke prevention in AF pending regulatory approval (approval in Europe obtained in November 2012, after publication of 2012 ESC update).
‡ The 2012 CCS focused update recommended apixaban once approved by Health Canada (approved December 2012).

stroke and systemic embolism in patients with nonvalvular AF, the ACCF/AHA/HRS now recommends that dabigatran is a useful alternative to warfarin to reduce the risk of stroke and systemic embolism in patients with nonvalvular AF.[4] Dabigatran etexilate is a prodrug that is rapidly converted to an active direct thrombin (factor IIa) inhibitor. Unlike warfarin, which undergoes predominantly hepatic elimination, dabigatran is excreted renally. For patients with a creatinine clearance of >30 ml/min, the approved dose is 150 mg twice daily. For patients with a creatinine clearance of 15 to 30 ml/min, the approved dose is 75 mg twice daily. These recommendations regarding dabigatran were largely based on the results from the Randomized Evaluation of Long-term anticoagulant therapy (RE-LY) study—a multinational, parallel-group, randomized controlled trial comparing 2 blinded doses of dabigatran (110 and 150 mg twice daily) with open label warfarin (dosed to a target international normalized ratio of 2 to 3) in patients with AF and ≥1 additional stroke risk factor.[45] The results from that study indicated that dabigatran 150 mg was superior to warfarin for the prevention of ischemic stroke and systemic embolism (dabigatran 150 mg, RR 0.65, 95% CI 0.52 to 0.81, $p < 0.001$ for superiority) with a similar rate of major bleeding (3.57% with warfarin; 3.32% with 150 mg dabigatran). The patients randomized to dabigatran 110 mg experienced fewer major bleeding episodes than the warfarin group, and this dose was noninferior for stroke reduction (dabigatran 110 mg, RR 0.91, 95% CI 0.74 to 1.11, $p < 0.001$ for noninferiority). The rates of intracranial hemorrhage were lower with dabigatran than with warfarin ($p < 0.001$ for both doses of dabigatran compared with warfarin).

Dabigatran is also licensed for use in Canada. The CCS has recommended dabigatran in preference to warfarin, with the possible exceptions of patients with a propensity to dyspepsia or gastrointestinal bleeding and those at substantial risk of coronary events. The guidelines recommended 150 mg twice daily for most patients and 110 mg twice daily for patients ≥80 years old or patients with a low body weight, decreased renal function, or an increased risk of major bleeding.[6] (The 110-mg dosage form of dabigatran is not available in the United States.)

For cases in which oral anticoagulation therapy is recommended, the ACCP guidelines suggest dabigatran 150 mg twice daily rather than vitamin K antagonist therapy, with the exception of patients with AF and mitral stenosis, stents, or $CHADS_2$ ≥1 who experience an acute coronary syndrome. The guidelines noted that clinicians should be aware that no antidote is available for dabigatran.

The ESC guidelines were published before the approval of dabigatran in Europe (approved August 2011). The 2012 focused update to the ESC guidelines recommended dabigatran in preference to warfarin for stroke prevention in AF.[30] The guidelines used the HAS-BLED (Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile international normalized ratio, Elderly, and Drugs/alcohol; Table 5) bleeding risk scoring system and stroke risk to stratify the recommendations for thromboprophylaxis.[13] If a patient has a low risk of bleeding (e.g., HAS-BLED score 0 to 2), dabigatran 150 mg twice daily is recommended; if a patient has a greater risk of bleeding (e.g., HAS-BLED score ≥3), dabigatran 110 mg twice daily is recommended.

New Recommendations for Rivaroxaban and Apixaban

Since the publication of the guidelines, rivaroxaban was approved for use in the United States, Canada, and

Europe.[30,46,47] In 2012, the ECS and CCS both published focused updates to their guidelines, recommending rivaroxaban in preference to warfarin for stroke prevention in patients with AF. Although rivaroxaban was not shown to be superior to warfarin, the double-blind Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET AF) trial demonstrated that rivaroxaban was noninferior to warfarin for the prevention of stroke or systemic embolism (rivaroxaban, HR 0.79, 95% CI 0.66 to 0.96, p <0.001 for noninferiority).[48] Significantly, the rivaroxaban group had similar rates of major bleeding (HR 1.03, 95% CI 0.96 to 1.11, p = 0.44) and significant reductions in intracranial hemorrhage (0.5% vs 0.7%, p = 0.02) and fatal bleeding (0.2% vs 0.5%, p = 0.003) compared with the warfarin group. The use of rivaroxaban was not yet covered by the ACCF/AHA/HRS or the ACCP.

The ESC and CCS focused updates noted that apixaban is also recommended in preference to warfarin, pending regulatory approval (approved in Europe in November 2012 and approved in Canada in December 2012).[30,47] This recommendation was based on the results from the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) and the Apixaban Versus Acetylsalicylic Acid to Prevent Strokes in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment (AVERROES) double-blind trials.[49,50] The ARISTOTLE trial demonstrated that apixaban was superior to warfarin in preventing stroke or systemic embolism (apixaban, HR 0.79, 95% CI 0.66 to 0.95, p <0.001 for noninferiority, and p = 0.01 for superiority), caused less bleeding (HR 0.69, 95% CI 0.60 to 0.80, p <0.001), and resulted in lower mortality (HR 0.89, 95% CI 0.80 to 0.99, p = 0.047) in patients with AF.[50] The AVERROES trial showed that in patients with AF for whom warfarin therapy was unsuitable, apixaban reduced the risk of stroke or systemic embolism (apixaban, HR 0.45, 95% CI 0.32 to 0.62, p <0.001) without significantly increasing the risk of major bleeding (apixaban, HR 1.13, 95% CI 0.74 to 1.75, p = 0.57) or intracranial hemorrhage (apixaban, HR 0.85, 95% CI 0.38 to 1.90, p = 0.69).[49] Apixaban was approved for use in the United States in December 2012; however, its use is not yet covered in the ACCF/AHA/HRS or ACCP guidelines.

Additional Updates to ESC, ACCP, and CCS Guidelines

The ACCF/AHA/HRS, CCS, and ACCP guidelines have recommended the $CHADS_2$ index for primary risk assessment and selection of antithrombotic therapy (Table 6). The $CHADS_2$ risk factors include congestive heart failure, hypertension, age ≥75 years, diabetes, and previous stroke/transient ischemic attack/thromboembolism. Each risk factor is assigned 1 point, except for stroke/transient ischemic attack/thromboembolism, which is assigned 2 points. The ACCF/AHA/HRS noted that the $CHADS_2$ index is simple and easy to use, with broad applicability.[6] However, the ACCP noted that for patients with a $CHADS_2$ score of ≤1, the presence of multiple non-$CHADS_2$ risk factors for stroke (e.g., age, sex) might favor oral anticoagulation therapy rather than no therapy or aspirin.

The ESC has now recommended the CHA_2DS_2-VASc for assessment of stroke risk in patients with AF. This risk scheme expands the $CHADS_2$ index with the following risk factors for stroke: vascular disease, age (65 to 74 years), and sex category (female sex). Additionally, the $CHADS_2$ factor of age ≥75 years carries more weight (2 points) in the CHA_2DS_2-VASc.

The ESC and CCS guidelines have also recommended the use of the HAS-BLED scoring system (Table 5) to evaluate the risk of bleeding. A HAS-BLED score of ≥3 indicates a high risk of bleeding with thromboprophylaxis.

The ESC also created the new category "longstanding persistent AF" to describe AF persisting ≥1 year yet the physician has determined that the pursuit of a rhythm-control strategy is reasonable. This category is between persistent and permanent AF and was added to better recognize these patients as candidates for nonpharmacologic treatment strategies.[13,32]

The 2012 ESC focused update also included the use of vernakalant (approved in Europe September 2010) for the conversion of AF to sinus rhythm and interventional percutaneous left atrial appendage closure for patients with thromboembolic risk who cannot be managed in the long term with oral anticoagulation therapy.

Additionally, in the CCS focused update, accurate assessments of renal function and the recognition of comorbid chronic kidney disease has been recommended for patients with AF receiving oral anticoagulation therapy. These recommendations stipulate that patients with AF receiving oral anticoagulation therapy (1) should have their renal function assessed at least annually by measuring the serum creatinine and calculating their estimated glomerular filtration rate, (2) should be regularly considered for alteration of oral anticoagulant and/or dose changes according to the estimated glomerular filtration rate, and (3) should receive antithrombotic therapy that relates to the estimated glomerular filtration rate. The last should be done as follows: for patients with an estimated glomerular filtration rate >30 ml/min, the antithrombotic therapy should be similar to that for patients with normal renal function (i.e., according to their $CHADS_2$ score); and for patients with an estimated glomerular filtration rate of 15−30 ml/min and patients not receiving dialysis, the antithrombotic therapy should be determined according to their $CHADS_2$ score, except that the preferred agent for these patients is warfarin.

Conclusions

Overall, the ACCF/AHA/HRS, ESC, CCS, and ACCP guidelines are in general accord. However, where the guidelines differ, in addition to the obvious options and limitations (e.g., drug approval, available dosages), clinicians need to assess the individual patient's risk−benefit ratio. Patient preferences and circumstances should also be considered. Moreover, adequate thromboprophylaxis is vital to reduce AF complications. Thromboprophylaxis for stroke is greatly underused in patients with AF. In fact, a systematic review found that most studies of patients with AF with a previous stroke or transient ischemic attack reported treatment of <60% of eligible patients.[19] The newer guidelines and comprehensive risk stratification re-emphasize the available

management options and the importance of the early initiation of antithrombotic therapy.

In general, the current ACCP guidelines have recommended antithrombotic treatment less often and less strongly than previously (e.g., the recommendations tend to be weaker than in the previous ACCP guidelines). This trend is likely a result of the increased methodologic rigor of the current ACCP guidelines compared with previous ACCP guidelines. It is also consistent with the recommendations of MacLean et al,[51] who, in accordance with their findings that patient values and preferences regarding thromboprophylaxis treatment are highly variable, suggested that guideline panels should be circumspect in making strong recommendations (these findings are included in the current ACCP guidelines). In contrast, the ESC recommendations might result in more patients with AF receiving anticoagulation therapy, because of the use of the CHA_2DS_2-VASc score. The ESC has also recommended that management of certain therapies (i.e., dronedarone, catheter ablation) be supervised and/or performed by an experienced specialist. The ESC, ACCP, and CCS have made specific recommendations regarding triple therapy (aspirin, clopidogrel, and antithrombotic drugs) in patients with AF and stents; however, the ACCF/AHA/HRS guidelines only noted the increased bleeding risk with such treatment and the lack of prospective trials. The ACCF/AHA/HRS has recommended the use of dabigatran as an alternative to warfarin. The ESC, ACCP, and CCS have recommended dabigatran in preference to warfarin when oral anticoagulation therapy is indicated. Rivaroxaban was recently approved for use in the United States, Europe, and Canada. In the 2012 focused updates of their guidelines, the ESC and CCS have recommended *either* dabigatran or rivaroxaban in preference to warfarin.

Given that a large number of cases of stroke in patients with AF could be preventable through the use of appropriate thromboprophylaxis, these updated guidelines provide a valuable evaluation of recent scientific evidence for clinicians to evaluate the appropriate management options for their patients.

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